

Non-prescription analgesics and asthma

With the increase in the number of NSAIDs available in Australia without a prescription, more people will use such medications, increasing the potential for adverse reactions to occur in people sensitive to aspirin. Currently a number of these products are available in supermarkets etc. as well as in pharmacies

Pharmacists' responsibilities

Pharmacists train their staff to screen consumers who are purchasing over-the-counter analgesics, and refer these consumers to the pharmacist when appropriate. Pharmacists must personally take all reasonable steps to ascertain the therapeutic need and give directions for use to consumers who request products scheduled as Pharmacist Only Medicines. Consumers sensitive to aspirin need to be warned of the possibility of adverse reactions from commonly available pain relievers, low dose aspirin and cough and cold products as listed in Tables 1 and 2.

- It should be noted that adverse reactions may occur with topical products as well as oral forms.^{22<LE V>}
- A warning should be issued with the sale of many herbal products containing either salicylates or allergenic ingredients or contaminants. Teething gels containing choline salicylate are contraindicated in people with a known allergy to salicylates and should be used with caution in susceptible individuals.²³
- Low dose aspirin for the prevention of ischaemic stroke, transient cerebral ischaemic events or ischaemic heart disease should be used with the same caution in people with asthma.^{24<LE IV>} If antiplatelet therapy is necessary and aspirin cannot be taken, alternative therapies are available.

It is difficult to produce recommendations for the group of individuals with asthma who are without high-risk features and who have never been exposed to NSAIDs.²⁴

Table 1 Examples of Over-The-Counter Analgesics²³

Oral	Topical products
Aspirin, including low dose aspirin	Diclofenac
Diclofenac 25mg	Ketoprofen
Flurbiprofen 8.75mg	Ibuprofen
Ibuprofen 200mg	Methylsalicylate rubs
Ketoprofen 25mg	Piroxicam
Mefenamic acid 250mg	Salicylic acid-containing products
Naproxen sodium 220, 275mg	
Paracetamol	

Table 2 Examples of Combination Products containing Over-The-Counter NSAIDs

Aspirin/codeine combinations
Aspirin/dihydrocodeine
Ibuprofen combination products

Health professionals can consult *MIMS*, *APP Guide*, *AUS DI*, *Australian Medicines Handbook* or Medical Director for further information about brand names of products.

Labelling and consumer medicines information (CMI) should highlight the possibility of AIA with NSAIDS.

Adverse reactions should be recorded and reported to ADRAC.

This series on Asthma Topics for Health Professionals comprises eight separate titles:

- Asthma and Allergy
- Asthma and Lung Function Tests
- Asthma and Pain Relievers**
- Asthma and Air Pollution
- Asthma and Complementary Therapies
- Asthma and Infant Bedding
- Asthma and Diet in Early Childhood
- Asthma and Wheezing in the First Years of Life

To access these documents log on to:
www.NationalAsthma.org.au or contact the Department of Health and Ageing on **1800 500 053**.

Further information

National Asthma Council

The National Asthma Council website contains information and publications on asthma and has links to other asthma information sites www.NationalAsthma.org.au

Asthma Foundations of Australia

For further information on asthma and patient materials, contact your local Asthma Foundation on **1800 645 130**, or visit their websites:

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| www.asthma.org.au | www.asthmansw.org.au |
| www.asthmasa.org.au | www.asthmawa.org.au |
| www.asthmatas.org.au | www.asthmant.org.au |
| www.asthmaqld.org.au | www.asthmaaustralia.org.au |

Asthma www.health.gov.au/pq/asthma

HealthInsite www.healthinsite.gov.au

Australasian Society for Clinical Immunology and Allergy
www.allergy.org.au

Levels of evidence

- | | |
|--------------|---|
| I | Evidence obtained from a systematic review of all relevant randomised controlled trials |
| II | Evidence obtained from at least one properly designed randomised controlled trial |
| III-1 | Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method) |
| III-2 | Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies, or interrupted time series with a control group |
| III-3 | Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group |
| IV | Evidence obtained from case series, either post-test or pre-test and post-test |

The NHMRC levels of evidence ratings have been adapted from US Preventive Services Task Force (1989) *Guide to clinical preventive services: an assessment of the effectiveness of 169 interventions* (ed M Fisher), Williams and Williams, Baltimore, Appendix A, p 388.

Source: NHMRC
A guide to the development, implementation and evaluation of clinical practice guidelines.

References

- Medicines Control Agency, UK, October 22, 2002.
- Stevenson DD, Sanchez-Borges M, Szczeklik A. Classification of allergic and pseudoallergic reactions to drugs that inhibit cyclooxygenase. *Ann Allergy Asthma Immunology* 2001;87:177-180.
- Szczeklik A, Nizankowska E, Duplaga M. Natural history of aspirin-induced asthma. *Eur Respir J* 2000; 16: 432-436.
- Szczeklik A, Stevenson DD. Aspirin-induced asthma: advances in pathogenesis and management. *J Allergy Clin Immunol.* 1999 Jul;104(1):5-13.
- Jenkins C, Costello, J, Hodge L. (2003). Asthma and simple over-the-counter analgesics: An evidence-based review of the prevalence of aspirin-induced asthma and its implications for clinical practice. (BMJ – in press.)
- Vally H, Taylor ML, Thompson RJ. The prevalence of aspirin intolerant asthma (AIA) in Australian asthmatic patients. *Thorax* 2002;57:569-574.
- Stevenson DD, Hankammer MA, Mathison DA, Christiansen SC, Simon RA. Aspirin desensitization treatment of aspirin-sensitive patients with rhinosinusitis-asthma: long-term outcomes. *J Allergy Clin Immunol.* 1996 Oct;98(4):751-8.
- Settipane RA, Schrank PJ, Simon RA, Mathison DA, Christiansen SC, Stevenson DD. Prevalence of cross sensitivity with acetaminophen in aspirin sensitive asthmatic subjects. *J Allergy Clin Immunol* 1995; 96:480-5.
- Dahlen B, Szczeklik A, Murray JJ. Celecoxib in patients with asthma and aspirin intolerance. The Celecoxib in Aspirin-Intolerant Asthma Study Group. *N Engl J Med.* 2001 Jan 11;344(2):142.
- Stevenson DD, Simon RA. Lack of cross-reactivity between rofecoxib and aspirin in aspirin-sensitive patients with asthma. *J Allergy Clin Immunol.* 2001 Jul;108(1):47-51.
- Glasgow JFT and Middleton B. Reye syndrome – insights on causation and prognosis. *Arch Dis Child* 2001;85:351-353.
- De Almeida MAM, Gaspar AP, Carvalho FS, Nogueira A, Pinto JER. Adverse reactions to acetominophen, ASA and NSAIDs in children: what alternatives? *Allergy and Asthma Proc* 1977;18:313-318.
- Sansom L (Editor). Australian Pharmaceutical Formulary and Handbook 18th Edition. Pharmaceutical Society of Australia 2002; 164.
- Kemp C, McDowell J (Chief Editors). Paediatric Pharmacopoeia, 13th Edition. Pharmacy Department, Royal Children's Hospital Melbourne 2002.
- Fischer TJ, Guilfoile TD, Kesarwala HH, Winant JG, Kearns GL, Gartside PS, Moornaw CJ. Adverse pulmonary responses to aspirin and acetominophen in chronic childhood asthma. *Paediatrics* 1983;71:313-318.
- Lesko SM, Louik C, Vezina RM and Mitchell AA. Asthma morbidity after the short-term use of ibuprofen in children. *Pediatrics* 2002;109(2):1-4.
- Rachelefsky GS, Coulson A, Siegel SC, Stiehm. Aspirin intolerance in chronic childhood asthma: detected by oral challenge. *Pediatrics* 1975;56:443-448.
- Vedanthan PK, Menon MM, Bell TD, Bergin D. Aspirin and tartrazine oral challenge: incidence of adverse response in chronic childhood asthma. *J Allergy Clin Immunol* 1977;60:8-13.
- Botey J, Navarro C, Marin A, Eseverri JL. Aspirin-induced asthma in children. *Allergol et Immunopathol* 1988;16(3):145-149.
- Schuhl JF, Pereyra JG. Oral acetylsalicylic acid (aspirin) challenge in asthmatic children. *Clinical Allergy* 1979;9:83-88.
- Towns SJ and Mellis CM. Role of acetyl salicylic acid and sodium metabisulfite in chronic childhood asthma. *Pediatrics* 1984;73(5):631-637.
- ADRAC, case report, direct communication, August 2002.
- Caswell A (Ed) (2002) E-MIMs May 2002 MediMedia Australia Pty Ltd NSW.
- Levy S, Volans G. The use of analgesics in patients with asthma. *Drug Safety* 2001;24 (11) 829-841.

Asthma and Pain Relievers

An information paper for health professionals

This publication is dedicated to the memory of Professor Ann Woolcock AO

The aim of this paper is to provide an up-to-date, evidence-based summary of the issues around aspirin-induced asthma, including practical advice on assessment and treatment. A consumer brochure on this topic has also been developed. These documents have been produced by the Australian Government Department of Health and Ageing in collaboration with the National Asthma Council.

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Disclaimer

The information contained in this paper has been expert reviewed and represents the available published literature at the time of review. It is not intended to replace professional medical advice. Any questions regarding a medical diagnosis or treatment should be referred to a medical practitioner.



Introduction

Asthma is a common condition affecting 10% of adults and approximately 20% of children in Australia. However, asthma is not a homogenous entity, and many patterns and subtypes of asthma exist. Patterns may relate to

- frequency of symptoms (infrequent or frequent, episodic or persistent) or
- season (perennial versus seasonal asthma)

Subtypes of asthma also exist according to precipitating factors such as

- allergy (atopic versus non-atopic asthma)
- work exposure (occupational asthma)
- exertion (exercise-induced asthma) and
- infection (viral-induced asthma).

Asthma may also be classified according to

- severity (mild, moderate, severe, brittle or difficult) and
- response to treatment (steroid sensitive or resistant).

A certain pattern or subtype may occur as a predominant feature of an individual's asthma, but significant overlap of patterns or subtypes can occur. For example, in children the most common pattern is infrequent episodic asthma associated with respiratory tract infections, but this may co-exist with exercise-induced or seasonal asthma.

Key messages

- Aspirin-induced asthma (AIA) is a distinct clinical entity.
- The development of AIA does not depend on a person having had previous exposure to aspirin or NSAIDs (non-steroidal anti-inflammatory drugs)
- If a patient is already on regular aspirin or NSAIDs for other reasons, the diagnosis of AIA is very unlikely, and the medication should not be stopped.
- Aspirin-sensitive individuals may also be sensitive to paracetamol at high dose.
- Aspirin should not be used in children or adolescents under 16 years of age with febrile illness because of the association with Reye's syndrome.¹
- Both paracetamol and ibuprofen appear safe in most children, with no convincing evidence that either is more effective or harmful.

What is 'aspirin-induced asthma'?

Aspirin-induced asthma (AIA) is a distinct clinical entity and appears to be a specific subtype of asthma. It is characterised by asthma triggered within one to three hours of ingestion of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs). The asthma attack is often accompanied by or even preceded by symptoms of rhinitis (nasal obstruction, rhinorrhoea and sneezing) and facial flushing. The asthma attack triggered by aspirin and NSAIDs may be very severe and life threatening. The common feature of medications that trigger this reaction is their inhibition of the cyclo-oxygenase 1 (COX-1) enzyme.²

The clinical picture of this asthma syndrome differs from that of the majority of patients with childhood onset or allergic asthma. The initial onset of symptoms appears at an average age of 30 years, with rhinitis characterised by persistent watery rhinorrhoea, nasal obstruction and sneezing. Loss of a sense of smell, with development of troublesome nasal polyps (often requiring repeated nasal polypectomies), occurs in up to two thirds of patients. On average, asthma develops two years after the onset of rhinitis, with intolerance to aspirin and other NSAIDs occurring about four years later.³ Other names for this syndrome include Francis' Triad, Samter's Triad and the Aspirin Triad.⁴ As previously mentioned, it may co-exist with other patterns and subtypes of asthma.

Patients with AIA may often be unaware of their intolerance to aspirin. They may have taken aspirin or NSAIDs in the past, before onset of this syndrome, without any adverse reactions. However, in contrast to other types of allergies, the development of AIA does not depend on having had previous exposure to aspirin or NSAIDs. Although avoidance of all NSAIDs is important to prevent acute attacks, the condition tends to be progressive, despite avoidance of these medications. Avoidance of dietary salicylates has not been shown to improve the condition.

Other Terms for Aspirin-Induced Asthma (AIA)

- **Aspirin-sensitive asthma**
- **Aspirin-intolerant asthma**
- **NSAID-induced rhinitis and asthma**

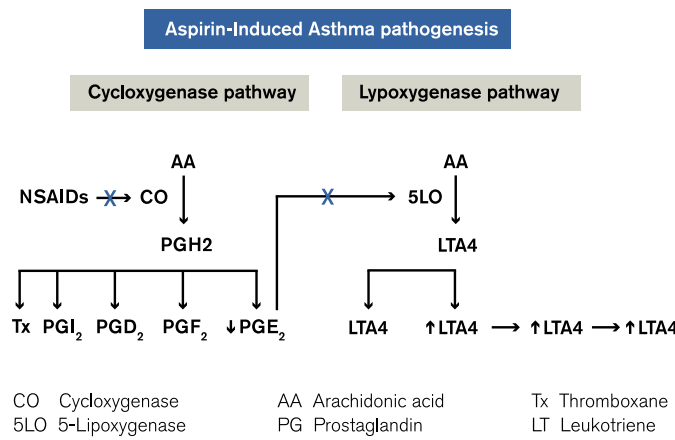
How common is aspirin-induced asthma?

Reports of the prevalence of this condition in adults with asthma have varied between 3-22%,⁵ depending on the diagnostic methods used. Recent Australian data based on questionnaires alone show that about 10-11% of adults with asthma report asthma triggered by aspirin or NSAIDs.⁶ However, prevalence by oral provocation testing was estimated at 22% in adults, 10% in children, according to a recent evidence-based review.⁵ The condition appears to be more common in patients with moderate to severe persistent asthma, particularly those with a history of nasal polyposis. Many of these patients are not atopic, and have increased baseline production of leukotrienes.

What is the mechanism of aspirin-induced asthma?

The central characteristic of these patients is their sensitivity to medications that inhibit the COX-1 enzyme. The COX enzymes produce a range of mediators that are responsible for regulating normal body functions (mainly COX-1) as well as inflammation, fever and pain (mainly COX-2). One of the mediators produced by COX-1 that regulates normal body function is prostaglandin E2. Evidence suggests that reduction of prostaglandin E2 levels by medications that inhibit COX allows activation of an enzyme pathway to produce increased amounts of inflammatory mediators called leukotrienes. These leukotrienes are responsible for many of the manifestations of an asthma attack, triggered in these patients by aspirin and NSAIDs.

Figure 1 The mechanism of aspirin-induced asthma



How is aspirin-induced asthma diagnosed?

The diagnosis can be made on history alone, if the patient has a history of asthma or rhinitis triggered within 1-3 hours of taking aspirin or NSAIDs. However, some patients with this condition may never have taken aspirin or NSAIDs. The clinical features of late-onset asthma, and prominent rhinitis with nasal polyposis increase the index of suspicion for AIA.

If the patient is already on regular aspirin or NSAIDs, the diagnosis of AIA is very unlikely, and the medication should not be stopped. Any suspicion of aspirin-induced asthma should be referred to an allergy specialist or respiratory physician for further assessment.

There are no blood tests or skin tests that will diagnose allergy to aspirin or NSAIDs. Confirmation of the diagnosis, if appropriate, requires controlled challenge with aspirin. This should only be done in a specialist clinic with appropriate resuscitation facilities.

How is aspirin-induced asthma treated?

In general, aspirin-induced asthma is managed in the same way as other types of asthma. Some patients with this condition may benefit from the addition of leukotriene receptor antagonist medication such as montelukast, but the response is variable and needs to be judged on an individual basis.

Desensitisation to aspirin is possible by graded introduction of aspirin and staying on a daily maintenance dose. In some patients, desensitisation improves nasal symptoms and asthma control and reduces the recurrence of nasal polyps. Desensitisation is also indicated if the patient requires aspirin or NSAIDs for cardiovascular prophylaxis or the treatment of arthritis. This should only be done under the supervision of a specialist with experience of the procedure.⁷

What pain relievers can patients with aspirin-induced asthma take?

Aspirin and NSAIDs are safe for the majority of people with asthma. Obviously, these medications should be avoided in patients with a positive diagnosis of aspirin-induced asthma, or where there is suspicion of the diagnosis.

Paracetamol is generally safe for patients with diagnosed or suspected aspirin-induced asthma. At high doses (more than 1000-1500mg per dose), paracetamol should be used with caution, as it can inhibit cyclooxygenase and cause mild asthma symptoms in some patients sensitive to aspirin.⁸

While the newer COX-2 inhibitors (selective NSAIDs), such as celecoxib and rofecoxib, have been used safely in patients with aspirin-induced asthma, occasional cases of anaphylaxis and drug-induced asthma have been reported.^{9,10} Unfortunately, elimination of dietary salicylates does not appear to improve asthma control, although compliance with the restrictive diet was doubtful in the one study examining this.²¹

Pain relievers and children with asthma

Aspirin is contra-indicated in children or adolescents under 16 years of age with febrile illness, not because of concerns about associated bronchospasm, but because of the association with Reye's syndrome (an acute illness producing inflammation of the brain and liver).¹ A decline in the incidence of Reye's syndrome has occurred since warnings were first issued about the possible role of aspirin in this syndrome.¹¹

Paracetamol can also be associated with bronchospasm in children with asthma. The effect appears to be dose-dependent, with the greatest risk observed for doses greater than 1500 mg of paracetamol per day.¹² Current Australian dose recommendations of 15-20mg/kg per dose for those under 12 years of age, or under 40-50kg in weight, should limit doses to well below this level.^{13,14}

In addition, approximately one third of salicylate-sensitive children with asthma will have cross-reactivity to paracetamol.¹² Reactions to paracetamol tend to occur later (i.e. 2-4 hours post-challenge) than those due to salicylates, and are less intense.¹⁵

Although both paracetamol and ibuprofen are widely used in Australia, there is a lack of published safety studies of their use in children with asthma. A recent study suggested that febrile asthmatic children treated with ibuprofen had a reduced risk of a subsequent outpatient visit for asthma compared to those treated with paracetamol. However, the study specifically excluded children with a known sensitivity to paracetamol, aspirin or any non-steroidal anti-inflammatory medication. Thus, in a selected group of asthmatic children at low risk for ASA, the relative risk for an asthmatic episode was lower for ibuprofen, compared to paracetamol.¹⁶ A prospective, randomised, double blind trial comparing paracetamol with ibuprofen in children with asthma is required before one of these two agents can be recommended over the other.

Naturally occurring salicylates are also present in many foods, and several studies have established that children with asthma can develop bronchospasm following oral salicylate ingestion. Prevalence rates for salicylate sensitivity in childhood asthma have varied from 13-28%, depending on dosage and the definition of what constitutes a significant response.^{17,18} Bronchospasm most often occurs within 30 minutes of ingestion, but can occur up to four hours after challenge.¹⁷ Unfortunately, elimination of dietary salicylates does not appear to improve asthma control, although compliance with the restrictive diet was doubtful in the one study examining this.²¹

Summary of safety in children

- Aspirin-containing medications are associated with Reye's syndrome, and therefore should be avoided in all children and adolescents under 16 with febrile illness.
- Both paracetamol and ibuprofen appear to be safe for the group of children with asthma but with no history of sensitivity or markers of risk for ASA (e.g. nasal polyps or angio-oedema). There is no convincing evidence currently in the medical literature to recommend one agent over the other.